REMARKS:

This response is filed in supplement to Applicants' amendment filed on February 6, 2004. To facilitate Examination, the arguments made in that amendment are repeated in the instant response where appropriate.

Claims 11, 13, 14, and 15 are cancelled without prejudice. Claim 1 is amended. Applicants believe that the specification provides adequate written description and enablement for all previously claimed antagonists, including oligonucleotides, peptides, non-peptidic compounds, and synthetic organic molecules, for the reasons stated in the previous responses submitted by applicants. However, in order to expedite prosecution and allowance of the instant application, applicants canceled claims 13, 14 and 15 directed to peptides, non-peptidic compounds, oligonucleotides and amended claim 1 to limit its scope to antibodies. Other antagonists of claim 1, including oligonucleotides, peptides, non-peptidic compounds, and synthetic organic molecules will be pursued in continuing applications.

New claims 68-73 are added in the instant amendment. Claims 65, 66 and 67 were added in the response of February 6, 2004. Discussion of claims 65-67 is reiterated here to facilitate examination. The subject matter of claims 65, 66 and 67 is the same as that of cancelled claim 11, and the subject matter of claims 69-73 is the same as that of originally filed claims 10, 12, 16, 17 and 18, respectively. Support for new claim 68 is found on page 4, lines 4-13 of the specification. The subject matter of new claim 68 is identical to that of the original claim 6. Claims 19, 26, 31, 35 and 39 were previously inadvertently marked as "withdrawn," and are now correctly marked as "cancelled." Minor changes are made to the specification. No new matter has been introduced. Claims 1-4, 6, 10, 12, 16-18, and 65-73 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

PRIORITY:

Claims 1-4, 6, 10, and 12-18 were afforded the effective filing date of January 6, 1999. The Examiner granted an effective filing date of January 6, 2000 to claim 11, because the Examiner believed that none of the provisional applications references all three monoclonal antibodies. Applicants respectfully disagree.

Claim 11 does not require a simultaneous availability of all three monoclonal antibodies, HUI77, HUIV26, and XL313, as alleged by the Examiner. Instead, claim 11 merely recites alternative types of monoclonal antibodies of the present invention ("...a monoclonal antibody having the binding specificity of monoclonal antibody HUI77, HUIV26, or XL313.") Antibody HUI77 was referenced in the provisional application No. 60/114,877 filed on January 6, 1999. Antibody HUIV26 was referenced in the provisional application No. 60/114,878 filed on January 6, 1999. Antibody XL313 was referenced in the provisional application No. 60/143,534 filed on July 13, 1999 and in the provisional application No. 60/152,496 filed on September 2, 1999. Thus, claim 11 should be afforded the effective filing date of at least July 13, 1999.

Furthermore, in order to simplify assignment of the effective filing date to the subject matter of claim 11, claim 11 is being replaced with new claims 65-67, each claiming a single antibody. Claim 11 is cancelled. Claim 65 is directed to antibody HUI77. Claim 66 is directed to antibody HUIV26. Claim 67 is directed to antibody XL313. In accordance with the discussion above, claims 65 and 66 should be afforded the effective filing date of January 6, 1999 and claim 67 should be afforded the effective filing date of July 13, 1999.

SPECIFICATION:

The specification is objected to because the term "effect" is used instead of the term "affect" on page 3, line 16. Applicants did not find the objected term on page 3 of the specification. Applicants believe that the Examiner's intention was to refer to

page 2, line 16, of the specification. Accordingly, applicants made the correction requested by the Examiner on page 2, line 16, of the specification as shown above.

CLAIM REJECTION – 35 U.S.C. § 112, FIRST PARAGRAPH:

The Examiner rejected claim 11 as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence that either the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials. This rejection is moot with respect to claim 11 due to the cancellation of the claim. With respect to claims 65-67, which incorporate the subject matter of claim 11, the rejection is traversed.

The specification provides adequate written description and enabling disclosure of the claimed antibodies as it describes methods for producing the antibodies and their specificity. In a recently decided case *Noelle v. Lederman et al.*, (Fed. Cir., 2004) No. 02-1187, the Federal Circuit has summarized the written description requirements with respect to antibodies as follows: "as long as an applicant has disclosed a 'fully characterized antigen,' either by its **structure, formula, chemical name, or physical properties**, or by depositing the protein in a public depository, the applicant can then **claim an antibody by its binding affinity** to that described antigen (*Id.* at page 12, emphasis added).

Here, monoclonal antibodies HUI77, HUIV26, and XL313 are claimed by their binding specificity to a particular antigen, a denatured collagen type-I (HUI77 and XL313) or denatured collagen type-IV (HUIV26). Since the antigens are characterized by their chemical name (*e.g.*, denatured collagen type-I and denatured collagen type-IV), according to the *Noelle* decision, applicants properly claimed the antibodies. Accordingly, claims 65-67 fully satisfy the written description requirement without a deposit of HUI77, HUIV26, and XL313.

With respect to the lack of enablement rejection, applicants would like to point out that ¶6 of the Office Action contradicts ¶7 of the Office Action, which

acknowledges that the specification is "enabling for the antagonists, designated monoclonal antibodies HUI77, HUIV26, and XL313 binding denatured collagen for the inhibition of angiogenesis." Accordingly, the lack of enablement rejection under ¶6 is improper and should be withdrawn.

The Examiner maintained the rejection of claims 1-4, 6, and 10-18 under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for monoclonal antibodies HUI77, HUIV26, and XL313, allegedly, does not provide enablement for other embodiments of antagonists encompassed by the claims. The Examiner appears to believe that because the specification provides only examples of three specific antibodies, HUI77, HUIV26, and XL313, inhibiting angiogenesis and because "[a]pplicants have not provided any evidence that suggests that other monoclonal antibodies, polyclonal antibodies, non-peptidic compounds, cyclic peptides or oligonucleotides would have the same inhibitory effect," undue experimentation would be required in order to practice all embodiments of the invention.

With respect to non-peptidic compounds, cyclic peptides, and oligonucleotides, this rejection is moot in view of amendments to claim 1 and cancellation of claims 13-15. As explained above, amended claim 1 is directed to **antibodies** having a binding specificity toward a denatured collagen. Other antagonists of claim 1 will be pursued in continuing applications.

With respect to antibodies, applicants respectfully traverse this rejection. Applicants submit that the specification fully satisfies the requirement for enablement under 35 U.S.C. § 112, first paragraph. First, as discussed above, *Noelle* allows claiming antibodies by their binding affinity to a described antigen, such as a denatured collagen. Accordingly, instant claims 1-4, 6, 10, 12 and 16-18 properly claim antibodies by their specificity to a denatured collagen.

Second, "[t]he law does not require a specification to be a blueprint in order to satisfy the enablement requirement," *Staehlin v. Secher*, 24 U.S.P.Q. 2d 11513, 1516 (Bd. Pat. App. &Int. 1992). A specification need not describe—and best

omits—that which is well known in the art. *See, e.g., In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). It is also well-settled in the law that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982).

The Examiner argues that "[a] number of antibodies may possess a high affinity for the denatured collagens but not be effective in inhibiting angiogenesis." Applicants disagree.

It is a discovery of the inventors that antagonists, such as antibodies, that specifically bind to a denatured collagen with higher affinity than to the native collagen block angiogenesis. More specifically, the instant specification discloses that the antagonists recognize cryptic epitopes in collagens (page 3, lines 15-18). Since a denaturation of collagens exposes cryptic epitopes, the antagonists of the present invention bind to denatured collagens with higher affinity than to the native collagen (page 15, lines 18-24; page 16, lines 4-16). The specification also discloses that the difference in the binding affinities of antagonists with denatured and native collagens is at least 3-fold, preferably 5-fold, and even more preferably 10-fold (page 16, lines 5-16). Furthermore, the specification explains that a number of conventional screening methods can be used to identify antagonists with specificity for denatured, but not native forms of collagen (pages 16-17). For example, antagonists of the present invention may be identified by a binding assay (page 17, lines 2- 22) and may be further screened by an angiogenesis assay (pages 17-19). These methods are discussed in more detail with respect to isolation of claimed antibodies (pages 19-24).

Also, the specification provides specific examples of using the general methods and criteria set forth in the instant specification to arrive at, not one, but three antibodies, HUI77, HUIV26, and XL313, having the required specificity for a denatured collagen. Therefore, sufficient and reasonable amount of guidance is

given by the specification and it would be only a routine matter for one of skill in the art to conduct screening for additional antibodies with specificity for denatured collagen. The experimentation (screening) that is required to isolate additional antibodies is merely routine, not an invitation to research and discover as alleged by the Examiner. Indeed, the instant specification, not the knowledge of one skilled in the art, supplies the novel aspect of an invention - selection of antagonists capable of inhibiting angiogenesis, wherein the selection is based on antagonist's specific affinity to denatured collagens.

Thus, one skilled in the art would be able to practice the claimed embodiments without undue experimentation in light of the teachings of the instant specification. Consequently, applicants submit that claims 1-4, 6, 10-12 and 16-18 are enabled by the specification and that the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

CLAIM REJECTION – 35 U.S.C. § 112, SECOND PARAGRAPH:

The Examiner has rejected claims 1-4, 6 and 10-18 under 35 U.S.C. § 112, second paragraph on the grounds that the "recitation 'denatured collagens' in claims 1-4, 6 and 10-18 is vague and indefinite." Applicants respectfully traverse the rejection.

Applicants would like to point out that the Examiner made exactly the same rejection in the Office Action dated October 2, 2001 (¶16(a)). The rejection was withdrawn in the Office Action of April 23, 2002 (¶7) in view of the applicants' arguments. Thus, applicants believe that the rejection was made in error in the present Office Action. Nevertheless, for the Examiner's reference, applicants include their earlier arguments:

The Examiner's attention is drawn to the following section of the specification discussing "denatured collagens:"

> ***Denatured collagen refers to collagen that has been treated such that it no longer predominantly assumes the native triple helical form.*** Denaturation can be accomplished by heating the

> collagen. In one embodiment, collagen is denatured by heating for about 15 minutes to about 100°C. Denaturation can also be accomplished by treating the collagen with a chaotropic agent. Suitable chaotropic agents include, for example, guanidinium salts. Denaturation of a collagen can be monitored, for example, by spectroscopic changes in optical properties such as absorbance, circular dichroism or fluorescence of the protein, by nuclear magnetic resonance, by Raman spectroscopy, or by any other suitable technique. Denatured collagen refers to denatured full-length collagens as well as to fragments of collagen. A fragment of collagen can be any collagen sequence shorter than a native collagen sequences. For fragments of collagen with substantial native structure, denaturation can be effected as for a native full-length collagen. Fragments also can be of a size such that they do not possess significant native structure or possess regions without significant native structure of the native triple helical form. Such fragments are denatured all or in part without requiring the use of heat or of a chaotropic agent. The term denatured collagen encompasses proteolyzed collagen. Proteolyzed collagen refers to a collagen that has been fragmented through the action of a protecolytic enzyme. In particular, proteolyzed collagen can be prepared by treating the collagen with a metalloproteinase, such as MMP-1, MMP-2 or MMP-9, or by treating the collagen with a cellular extract containing collagen degrading activity or is that which occurs naturally at sites of neovascularization in a tissue. (Specification page 14, line 27 to page 15, line 17.)

Therefore, applicants believe that the objected term is clearly defined by the specification.

Also, the Examiner has rejected claims 1-4 under 35 U.S.C. § 112, second paragraph for the recitation of the terms "collagen" and "collagens." Applicants respectfully traverse the rejection.

The present invention is directed to antagonists selected by their specificity to denatured collagens over native collagens. Thus, as explained on page 14, lines 20-25, the invention can be used with any collagens, which are broadly defined as extracellular matrix proteins containing a $[Gly\text{-}Xaa\text{-}Xaa]_n$ sequence. Even though the "collagen superfamily" includes many collagen types, as pointed out by the Examiner, as long as one can obtain a denatured and a native form of a given

collagen, he would be able to practice the instant invention by selecting antigens with a specificity toward the denatured form, as taught by the instant specification.

Accordingly, those skilled in the art will readily recognize that the terms "collagen" and "collagens" refer to compounds of the "collagen superfamily." Since "a specification need not describe—and best omits—that which is well-known in the art" (See, e.g., *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991)), the objected terms are not indefinite, because a reasonable amount of guidance is given by the specification so that it would be only a routine matter for one of skill in the art to apply the present invention to various types of collagens.

Also, the Examiner has rejected claim 1 under 35 U.S.C. § 112, second paragraph for the recitation of term "substantially reduced affinity." The Examiner appears to believe that the metes and bounds of the claim cannot be determined because "[t]he claim does not clarify what is regarded as limited affinity or what this reduced affinity is compared to." Applicants respectfully traverse the rejection.

The specification defines the term "substantially reduced affinity" on page 16, lines 4-16, of the specification. In particular the specification states:

> A "substantially reduced affinity" is an affinity of about 3-fold lower than that for the denatured collagen, more preferably about 5-fold lower, and even more preferably about 10-fold lower.

Additionally, the claim language specifies that a binding affinity of antagonist to a denatured collagen is compared to a binding affinity of antagonist to a native triple helical form of a collagen. Thus, the term "substantially reduced affinity" is defined by the specification as an affinity which is at least 3-fold lower than an affinity to which it is compared. Also, the claim language clearly indicates that the reduced binding affinity of an antagonist for native collagen is determined by comparing the antagonist's affinity for the native collagen with that for the denatured form of the same collagen. In view of the above, applicants request a withdrawal of the rejection under Section 112, second paragraph.

CLAIM REJECTION – 35 U.S.C. § 102:

Claims 1-4 and 6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brooks *et al.*, J. Clin. Invest. 96: 1815-1822, October 1995 (Brooks-95) as evidenced by Brooks *et al.*, Cell 85:683-693, 1996 (Brooks-96). In an interview held on July 16, 2004, the Examiner agreed to drop the § 102 art rejections (Interview Summary, 7/10/04).

Applicants explained in the interview that with respect to the antibody LM609, its specific affinity is directed to integrin αvβ3 and not denatured collagen, as required by the instant claim 1. There is nothing in Brooks-95 describing antagonists targeting denatured or proteolyzed collagens. Therefore, Brooks-95 does not explicitly anticipate the instant claim 1.

LM609 does not inherently anticipate the instant claim 1. The most recent inherent anticipation standard articulated by the Federal Circuit in *Schering Corp. v. Geneva Pharmaceuticals*, 339 F.3d 1373 (Fed.Cir. Aug. 1, 2003), asks whether a prior art device ***necessarily contains*** the omitted feature based on the current knowledge of those skilled in the art. The fact that integrin αvβ3 selectively binds to the denatured collagens and LM609 is specific to the integrin αvβ3 does not necessarily mean that LM609 will selectively bind to the denatured collagen. Biomolecules have numerous binding sites with different affinities and 3-D configurations. The binding site of integrin αvβ3 to the denatured collagen is likely to be completely different from that for binding LM609. Thus, binding of integrin αvβ3 to the denatured collagen and to LM609 does not necessarily mean that LM609 will also bind to denatured collagen with the required specificity. Therefore, Brooks-95 does not anticipate the instant claim 1 as alleged by the Examiner.

Brooks-95 does not make claim 1 obvious. The antagonists of the present invention specifically bind to a denatured collagen with a higher affinity than to the native form of the collagen. The difference in the affinities is at least about 3-fold (page 16, lines 4-16).

Brooks-95, teaches that "**antagonists of integrin αvβ3** [not antagonists of denatured collagen] may provide a novel approach for the treatment of malignant

breast tumors" (page 1815, right column, second paragraph). In fact, the specific affinity of monoclonal antibody LM609 referenced by the Examiner is directed to integrin $\alpha v\beta 3$ and not denatured collagen. Based on the teachings of Brooks, one skilled in the art would not have attempted to develop antibodies with a specificity to denatured collagen. Therefore, claim 1 is neither anticipated nor rendered obvious by Brooks-95 and Brooks-96. Claims 2-4 and 6 depend from patentable claim 1 and are therefore believed to be patentable for at least the same reasons as claim 1.

Claim 11 is rejected under 35 U.S.C. 102(a) as being anticipated by Petitclerc *et al.* (Cancer Research 59:2724-2730, June 1, 1999). This rejection is moot with respect to claim 11 due to the cancellation of the claim.

The Petitclerc article does not constitute prior art with respect to new claims 65-67. Since the cited reference discloses only antibody HU177, the reference is not relevant with respect to claims 66 and 67 that are directed to different antibodies. The cited reference does not constitute prior art with respect to claim 65, because the effective filing date of this claim is January 6, 1999, which is prior to the publication date of the cited reference (June 1, 1999).

ELECTION OF SPECIES IN A PRIOR RESPONSE:

In view of the long prosecution history of the instant patent application, applicants would like to remind the Examiner that original claim 6 was directed to five specific types of the denatured collagen (types I-V). In response to the election requirement of October 2, 2001, applicants chose collagen type-I as the species for examination and claim 6 was amended to limit its scope to collagen type I antigen. New claim 68 recaptures the scope of original claim 6 to provide a correct antecedent basis for claim 66, which claims a monoclonal antibody having the binding specificity of monoclonal antibody HUIV26. This antibody specifically binds only to denatured collagen type-IV.

New claim 68 is consistent with the instant specification, which states that antibodies of the present invention may have specificity for denatured collagen of type-I, -II, -III, -IV, -V, or their combinations (page 4, lines 4-13). As explained in the specification and figures, HUI77 specifically binds denatured collagens type-I, -II, -III, -IV, and -V but binds to native collagens type-I, II, -III, -IV, and V with substantially reduced affinities (Figure 2 and page 38, lines 15-26). HUIV26 specifically recognizes denatured collagen type-IV but binds to native collagen type-IV with substantially reduced affinity (page 41, lines 13-18). Thus, claims 65 and 66, that depend from claim 10, have been amended to also be dependent on new claim 69, which depends in turn from new claim 68. XL313 specifically recognizes denatured collagen type-I but does not react with the native triple helical form of collagen type I (page 45, lines 12-20). Claim 67, which depends from claim 10, has also been amended to depend from claim 69.

During an interview on July 19, 2004, the Examiner indicated that claim 1, if limited to type I collagen, is allowable. Applicants respectfully submit that 37 C.F.R. § 1.146 and MPEP §§ 808 and 809 demand from the Examiner search and consideration on the merits the non-elected species, collagens types II-V.

Section 1.146 describes selection of species and is interpreted in MPEP §§ 808 and 809. MPEP 808.01(a) provides: "In all applications where a generic claim is found allowable, the application should be treated as indicated in MPEP §809.02(b), §809.02(c), or §809.02(e)." MPEP 809.2(c) describes the course of action appropriate in the present case:

> (B) When **a generic claim is subsequently found to be allowable**, and **not more than a reasonable number of additional species are claimed**, treatment shall be as follows: (1) When *all* claims to each of the additional species are embraced by an allowable generic claim as provided by 37 CFR 1.141, applicant **must** be advised of the allowable generic claim and that **claims drawn to the nonelected species are no longer withdrawn** since they are fully embraced by the allowed generic claim. (emphasis in bold is added)

The language used in MPEP 809.02(c) is consistent with the language used by the Patent Board of Appeals and Interferences in *Ex Parte Julian Wallace*, Appeal No. 94-33, 1994 WL 1687118, 2 (Bd.Pat.App. & Interf. 1994). The Patent Board stated:

> Additionally, the proper procedure to follow when an election of species is required and applicants' elected species is not found in the prior art, is to **search thereafter a reasonable number of non-elected species representative of the generic invention**. (emphasis added)

The phrase "reasonable number" is also used in the language of 37 CFR § 1.146 and MPEP 809.02(c). Although there does not appear to be caselaw interpreting the term "reasonable," well-known and respected patent law reviews note that **at least five species** is in the range of what is to be considered a reasonable number, in light of the 1978 amendments to Sections 1.141 and 1.146. *Chisum on Patents*, Vol. 4, Ch. 12, § 12.03(3) n.1, 2.

Combining these authorities, applicant submits that there is a defined procedure for dealing with applications in which the Office has required the Applicant to elect a species for prosecution. The procedure requires that the Office proceeds in searching and reviewing on the merits claims drawn to a reasonable number of non-elected species once a generic claim that embraces those species is identified as allowable.

Turning to the present application, applicants submit that claim 1 is a generic claim that reads on the elected species (type-I denatured collagen). Claim 1 also reads on a reasonable number of additional species (four types of denatured collagen – types II-V as claimed in new claim 68). All claims directed to the additional species (claims 65-73) depend from and, thus, are embraced by claim 1. Therefore, once generic claim 1, as directed to collagen type I, is allowable, under MPEP 809.02(b), claim 1, as directed to the additional four species of collagen, should be searched and studied by the Examiner on the merits.

Furthermore, new claims 65-73, directed to collagens types I-V, should be searched and studied on the merits. In addition to the requirement for consideration of additional species under MPEP 809.02(b), generic claim 1 is already fully supported by the subject matter presented by the Applicant in the description. As stated above, antibody HUI77 specifically binds denatured collagens type-I, -II, -III, -IV, and -V while binding to native collagens type-I, -II, -III, -IV, and V with substantially reduced affinities. HUIV26 specifically binds denatured collagen type-IV, but binds native collagen type IV with reduced affinity, and XL313 specifically binds denatured collagen type-I, but binds native collagen type-I with reduced affinity. Therefore, antagonists of the additional species of generic claim 1 are supported by the specification as filed and these species are entitled to consideration on the merits.

REJOINDER OF PRODUCT AND PROCESS CLAIMS:

In the Office Action dated October 2, 2001, the Examiner noted that "[m]ethod claims limited to the scope of the allowable product claims should be rejoined and examined at the time the product claims are indicated as being allowable." Office Action, page 2. In the July 16, 2004 interview, the Examiner indicated that the claims should be rejoined at the time claim 1 becomes allowable. Applicants therefore remind the Examiner to rejoin and examine the withdrawn method claims of Group II (claims 20-25, 27-30, 32-34, 36-38, 40-42, and 60-64) when product claim 1 becomes allowable.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Dated: August10, 2004

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